

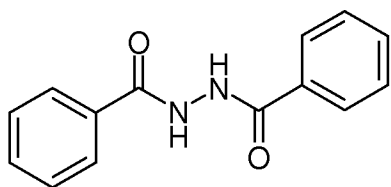
REMARKS

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication that claims 40-42 and 44-46 recite allowable subject matter.

Amendments

Claims 1-2, 10-12, 16-18, 29, 32, 36, 43-46 are cancelled. The compound claims are amended to be directed to compounds having the following core structure:

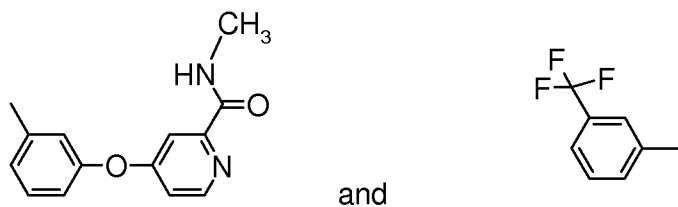


See, e.g., claim 3. In addition, the claims are amended to use language in accordance with conventional US practice, and dependent claims are amended to be consistent with the language of amended claim 3.

Claim 9 is amended so as not to expressly refer to Tables 1 and 2 of the specification. Claims 9 now recites diacylhydrazine compounds from table 1 using definitions of Groups A and B. Compounds from table 2 are now recited in new claim 49. New claim 48 relates to subject matter cancelled from claim 20. New claims 50 and 51 are directed to non-solvate forms of the compounds.

Election and Withdrawn Claims

In response to the Lack of Unity Objection/Restriction, applicants hereby elect Group I, wherein L' is pyridine. Claims 3-9, 13, 14, 37-42, 47 and 49 read on the elected invention. As for the further election of a single disclosed species, applicants hereby elect compound 44 as shown in the Table at page 68. In this compound, D of formula I is -CO-NH-NH-CO-, and A and B are respectively,



Within the claims of the elected group, claims 3-6, 8, 9, 13, 14, 37-42, 47 and 49 read on the elected species. The Lack of Unity Objection/Restriction is, however, respectfully traversed.

In support of the Lack of Unity Objection as to the Markush claims, the Examiner refers to “Markush Practice” as described in Annex B of the PCT rules. Referring to Annex B, Part 1(f), the Examiner argues that if one of the Markush alternatives is not novel over the prior art, then unity of invention shall be reconsidered by the Examiner.

The Examiner then asserts that the compound benzoic hydrazide is in the prior art, citing an excerpt from the 1992 Aldrich catalog, and that this compound is one of applicants’ Markush alternatives **for claim 34**. However, even if correct, this assertion would only apply to the Markush group recited in claim 34.

The compound cited by the Examiner, benzoic hydrazide, has the formula $C_6H_5CONHNH_2$, as indicated in the Aldrich catalog. This compound does not fall within the scope of any one of Groups I-III and VI presented at page 5 of the Office Action. Thus, the cited compound provides no support for the assertion that the combined subject matter of Groups I-III and VI lack unity of invention. To state it another way, the compound cited by the Examiner does not support an assertion that the Markush group recited in independent claim 3 (claims 1 and 2 have been cancelled) lacks unity of invention. Thus, the Examiner has not set forth a basis for reconsidering unity of invention as to applicants’ Markush compound claim 3, and the claims dependent thereon.

With respect to process/method Groups VII and VIII, , Rule 13.1 permits combinations of claims directed to a given product, a process specially adapted to the manufacture of the product, and claims directed to the use of the product. The Lack of Unity Objection/Restriction presents no rationale as to why, in light of Annex B, Part 1(e), the claims of Groups VII and VIII are said to lack unity with the compound claims under Rule 13.1.

In view of the above remarks, withdrawal of the Lack of Unity Objection/Restriction

as to Groups I-III, VI and VII-VIII is respectfully requested.

Rejection of claims 1-2 under 35 USC 112, second paragraph

Claims 1-2 are rejected as allegedly being indefinite. This rejection is rendered moot by the cancellation of claims 1-2. Cancellation of these claims is not to be construed as acquiescence to this or any other ground of rejection. Withdrawal of the rejection is respectfully requested.

Rejection of claim 10 under 35 USC 112, second paragraph

Claim 10 is rejected as allegedly being indefinite. This rejection is rendered moot by the cancellation of claim 10. Cancellation of this claim is not to be construed as acquiescence to this or any other ground of rejection. Withdrawal of the rejection is respectfully requested.

Rejection of claims 1-8, 10, 14, 36-39, 43 and 47 under 35 USC 112, first paragraph

Claims 1-8, 10, 14, 36-39, 43, and 47 are rejected as allegedly lacking enablement under 35 USC 112, first paragraph. This rejection is respectfully traversed.

Applicants gratefully acknowledge the Examiner's indication that the "variables in claim 6, with a definition of R⁹ as H" are enabled, as well as the R⁸ groups O-alkyl-NH₂ and S-alkyl. It is noted that claim 6 depends from claim 5 and the latter defines q as 0. Thus, in claim 6, R⁹ is defined as H.

It is by now well settled law that enablement under 35 USC §112, first paragraph, only requires objective enablement. See, e.g., *In re Marzocchi et al.*, 169 USPQ 367, 369(CCPA 1971):

The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

An application disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance

with the enabling requirement of the first paragraph 35 U.S.C. §112, unless there is reason to doubt the objective truth of statements contained therein relied on for enabling support. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). *Fiers v. Revel*, 984 F.2d 1164, 24 USPQ2d 1601 (Fed. Cir. 1993). Furthermore, as stated in *In re Marzocchi*, the PTO must have adequate support for its challenge to the credibility of applicant's statements of utility. See also *In re Bundy*, 209 USPQ 48 (CPA 1981).

Also, it is by now well settled law that the test for enablement is not whether any experimentation is needed, but whether or not that experimentation is undue. See, *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable.

The present rejection does not present sufficient reasons or evidence to doubt the veracity of the objective enablement statements presented in the specification. Thus, the rejection does not satisfy the PTO's initial burden for making a lack of enablement rejection.

In the rejection, reference is made to the so-called Wands factors. It is noted that these factors are to be used to determine whether undue experimentation is involved. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). However, before the issue of undue experimentation arises, the PTO must present reasons to doubt the veracity of the objective enablement statements presented in an applicants' specification.

Initially, the rejection presents a reaction scheme which is said to represent the reaction procedure described at pages 157-161 of applicants' specification. See page 10 of the Office Action. However, it should be noted that this not the only description of a reaction procedure presented in the specification. At page 123, line 1 through page 136, line 20, the specification provides details on preparing compounds of formula I by reacting compounds of formula III with compounds of formula IV, and variations of this reaction procedure. As noted above, how enablement is set forth, either through the use of illustrative examples or by broad terminology, is of no importance.

The rejection then reproduces comments from the preface of the Dorwold text. This generalization is not directed to any particular chemical reaction or even a class of chemical reactions. Thus, this generalization would not provide one of ordinary skill in the art reasons to doubt the objective enablement of applicants' specification.

Thereafter, the Examiner alleges that reaction of phenols with bromopyridine to form

phenyl-pyridyl ethers has limitations as to tolerable substituents, citing page 589 of the March text (which discusses general a reaction $\text{ArBr} + \text{OR}^-$). However, the reaction scheme presented at page 10 of the Office Action does not involve bromopyridine. There is a reaction between hydroxybenzoic acid ethyl ester and (4-chloropyridine-2-carboxylic acid)-methyl amide, but the rejection does not refer to this reaction. Nor does the rejection indicate why one skilled in the art would believe that this reaction does not proceed. As for substituents, the rejection also does not consider the use of protecting groups or the introduction of substituents after the formation of a phenyl-pyridyl ether structure. See, e.g., page 133, line 15-page 135, line 2.

Contrary to the assertion in the rejection, the excerpt from page 589 of the March text does not refer to any requirements with respect para position or ortho position substituents on phenols reacted with ArBr . The rejection also asserts that pages 342-343 of the March text suggests that alkylhalide for applicants' R^8 group will yield cyclic ethers as a result of the phenyl-pyridyl ether formation, due to the Wilkinson ether synthesis. Firstly, in the reaction scheme shown at page 10 of the Office Action, R^8 would not be introduced by the reaction forming a phenyl-pyridyl ether, but would be introduced by a subsequent reaction. Secondly, it is unclear where the March text at pages 342-343 refers to alkylhalide yielding cyclic ethers.

Next, the rejection refers to the possibility of alkynes and alkenes undergoing addition of phenol, citing pages 684-685 of the March text. This portion of the text does refer to addition of alcohols and phenols to double bonds being catalyzed by acids or bases. The text does not indicate how prevalent such a reaction is, or whether it would even occur if there is a halogen for the phenol to react with instead. Moreover, this argument does not consider the introduction of substituents after the formation of a phenyl-pyridyl ether structure.

The rejection then refers intramolecular cyclization of phenols or phenolates with olefin substituents reacting to yield chromans (or perhaps coumaran was intended), citing the Hurd article, or benzofurans, citing the Buckle article. However, there is no suggestion that the conditions which Hurd et al. and/or Buckle et al. employed to obtain such reactions would be relevant to applicants' described reaction procedure. This argument also does not consider the well known use of protecting groups or the introduction of substituents after the formation of a phenyl-pyridyl ether structure, or to what extent such reaction would proceed when a

halogen atom is available for reaction with the phenol oxygen.

With respect to synthesis of the pyridyl-phenyl structure, the examiner cites the Dorwald text at page 298-299. Contrary to the allegation in the rejection, nothing in the cited text suggests that the mentioned cyclometallation reactions would occur to any relevant extent for the reaction of the 4-carboxybenzeneboronic acid and 4-bromo-pyridinium chloride starting materials employed in the reaction procedure described by applicants. As for the allegation of self-polymerization, there is nothing within the excerpt of page 41 of Dorwald text that suggests that applicants' reactants would be susceptible to such side reactions.

The rejection refers to the disclosure of Lowinger et al, particularly the results in table 23 for compounds 77 and 87, and asserts that "it is clear that if a substituent that is too large or not lipophilic enough, this leads to compounds with no activity." The data in Table does not support this conclusion. While "0" is listed for the activity of compound 87, having a phenyl substituent, compound 88 was active and had an even larger substituent, namely phenethyl. Non-alkyl substituents like NH₂ and NO₂ were also active. See compounds 85 and 86. Thus, the conclusion set forth in the rejection is not supported. It is also noted that the compounds in Table 3 have a different bridge group than that of applicants' compounds, and the bridge group connects a phenyl ring and a thiophene ring rather than two phenyl rings.

Reference is also made to Table 11 and a comparison of compounds 155 and 158. While there is a difference in activity between the position isomers 155 and 158, both compounds are active. As for compound 119, the loss of activity for this compound is said to be related to elimination of urea moiety. This provides no suggestion to doubt the enablement of applicants' compounds which possess a urea moiety.

As for the assertion of secondary amides substituents being disfavored in light of the disclosure of Khire et al., it is noted that compounds 2 and 8 were both active. Also, it is noted that the compounds in Table 3 have a different bridge group than that of applicants' compounds, and the bridge group connects a phenyl ring and an oxazole ring rather than two phenyl rings.

In view of the above remarks, it is respectfully submitted that the rejection fails to present sufficient evidence to support the assertion that the applicants' disclosure does not provide sufficient objectively enablement for one of ordinary skill in the art to practice the

invention without undue experimentation. Withdrawal of the rejection is respectfully requested.

Rejection of claims 1-4 and 9 under 35 USC 112, first paragraph

Claims 1-4 and 9 are rejected as allegedly lacking enablement under 35 USC 112, first paragraph. This rejection is respectfully traversed.

In the Office Action, it is alleged that one can not predict the stoichiometry of a particular solvate, e.g., whether $\frac{1}{2}$, one or 2 solvent molecules are incorporated. However, the Office Action is incorrect with respect to the alleged lack of enablement.

The cited article by West does not demonstrate that one of ordinary skill in the art in the field of pharmaceuticals would not know how to proceed in preparing solvates and how such solvates can be identified or characterized, e.g., by polarized light microscopy, etc. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) discussed supra.

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining “further trends and interrelations between molecular properties and solvate/hydrate formation.” See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled “Generation and Characterization of Solvates” on page 222, *Griesser* teaches that

Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies have been developed to speed up this process, allowing thousands of crystallization experiments in a short time.** (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. “The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation.” *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the “test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely

routine,” which it is in the present case.

In view of the above remarks, it is respectfully submitted that the rejection fails to present sufficient evidence to support the assertion that the applicants’ disclosure does not provide sufficient objectively enablement for one of ordinary skill in the art to practice the invention without undue experimentation. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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